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Cytokine profile as a prognostic tool in coronavirus disease 2019. Comment on “Urgent avenues in the treatment of COVID-19: Targeting downstream inflammation to prevent catastrophic syndrome” by Quartuccio et al.
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We read with interest the editorial ‘Urgent avenues in the treatment of COVID-19: Targeting downstream inflammation to prevent catastrophic syndrome’. As highlighted by Quartuccio *et al.*, using biomarkers to early identify patients at higher risk of clinical deterioration is crucial in choosing a suitable candidate for anti-cytokine therapy [1]. The timing and choice of the therapy is also key, since immunosuppressant strategies could impair the antiviral response. Serum cytokine levels have been associated with disease severity, but not much with short-term outcomes. To address this issue, we conducted a prospective cohort encompassing 109 COVID-19 adult non-ICU inpatients (NCT04320017).

Data was collected at hospital admission, and patients were categorized at day 14 (D14) according to the occurrence of death and/or ICU transfer. Inactivated plasma samples were tested for IL-1 β , IL-2, IL-4, IL-5, IFN γ , IL-6, IL-8, IL-10, IL-12p70, IL-22, IFN- β and TNF using high sensitivity kits. Patients’s baseline features and cytokine levels are presented in Table 1 and Table 2, respectively. At D14, 22.1% of patients were transferred to the ICU or died. Patients in this group had significantly higher baseline levels of IL-6, IL-8, TNF and IL-10. Those with baseline high viral load presented significantly higher levels of IL-10 (17.75 vs. 8.39 pg/ml, $P < 0.01$), IFN- γ (3.14 vs. 1.04 pg/ml, $P < 0.05$) and TNF (24.22 vs. 18.1 pg/ml, $P < 0.05$).

The immune phenotype of severe and critically ill COVID-19 patients is characterized by an impaired type I IFN response and hyper-inflammation [2,3]. In this regard, high baseline cytokine levels might be important prognostic biomarkers of the potentially lethal cytokine wave [2].

Herein, we evidenced that baseline inflammatory cytokines, notably IL-6, IL-8 and TNF, but also IL-10, correlate well with short-term clinical outcomes. This highlights not only the importance of their measurement as potential prognostic tools, but also provides crucial insights on timing and targets for immunosuppressant strategies. IL-6 is the most studied cytokine and its blockade was

Table 1
 Baseline features of COVID-19 patients and according to the outcome.

	All patients (n = 109)	ICU-free and alive at D14 (n = 81)	ICU admission or death (n = 23)
Demographic and comorbidity profile			
Male sex (%)	67 (62)	48 (59)	18 (78)
Age \geq 75 (%)	45 (41)	35 (43)	8 (35)
Hypertension (%)	63 (58)	45 (56)	15 (65)
Dyslipidemia (%)	42 (38)	30 (37)	11 (48)
Diabetes (%)	27 (25)	17 (21)	9 (39)
Ischemic heart disease (%)	27 (25)	20 (25)	7 (30)
Obesity (%)	18 (20)	14 (20)	3 (18)
Cancer (%)	26 (24)	20 (25)	5 (22)
eGFR $<$ 30 ml/min (%)	17 (16)	12 (15)	4 (17)
Lymphoma (%)	7 (6)	5 (6)	2 (9)
COPD (%)	7 (6)	5 (6)	2 (9)
Corticosteroids chronic use (%)	16 (15)	11 (14)	5 (22)
Clinical presentation			
Dyspnea (%)	65 (60)	42 (52)	18 (78)*
Respiratory rate \geq 24 breaths per min (%)	55 (52)	41 (52)	12 (57)
Fever \geq 38.8 °C (%)	20 (18)	15 (18)	3 (13)
SpO2 in room air, % (%)	93 [90–97]	93 [91–97]	91 [89–93]*
Supplemental oxygen (%)	77 (71)	53 (65)	20 (87)
Oxygen flow, L/min	3 [2–4]	2 [1–3]	3 [2–10]**
Laboratory findings			
Hemoglobin, g/dL	12.1 [11.2–13.6]	12.3 [11.4–13.6]	11.8 [11.1–13.9]
Neutrophils, /mm ³	4510–6020	4190–5570	5630 [3515–7445]*
Eosinophils, /mm ³	10 [0–50]	10 [0–60]	0 [0–20]*
Lymphocyte < 800/mm ³	73 (67)	24 (30)	11 (48)
Thrombocytes, $\times 10^3$	220 [153–288]	226.0 [160.0–285.0]	200.0 [117.5–301.5]
C-Reactive protein, mg/L	65.9 [28.4–108.6]	52.4 [17.4–104.0]	90.1 [57.0–251.0]**
Procalcitonin, ng/mL	0.1 [0.1–0.3]	0.1 [0.1–0.2]	0.3 [0.2–0.5]***
Ferritin, µg/L	895 [403–1538]	820 [341–1348]	1413 [689–2079]*
Troponin, ng/mL	16.4 [9.2–29.9]	14.7 [8.7–26.8]	20.2 [14.4–34.1]
Lactate dehydrogenase, U/L	355 [297–424]	340 [279–413]	377 [327–528]*
D-dimer, µg/L	1045 [550–1910]	930 [490–1840]	1370 [825–2200]
Low viral load# (%)	35 (34)	27 (36)	5 (22)
High viral load# (%)	14 (13)	8 (11)	5 (22)
Predominant pattern in chest CT scan			
Ground-glass opacities (%)	37 (38)	29 (40)	8 (38)
Consolidations (%)	50 (51)	38 (52)	9 (43)
Diffuse involvement (%)	9 (9)	4 (5)	4 (19)

Demographic, comorbidity and clinical and laboratory features at baseline for all patients and according to clinical outcome. Data was available at day 14 for 104 patients. Data are presented as counts (%) or medians [interquartile range].#Viral load from nasal swabs were performed in 104 patients, being considered low when superior to 30 cycle thresholds (ct), and high when inferior or equal to 20 ct. Comparisons across groups were performed with Mann-Whitney’s test for quantitative variables, and Fisher’s exact test for categorical variables, with P value < 0.05 considered as statistically significant (two-sided tests). Analyses were performed using GraphPad Prism 8. eGFR = estimated glomerular filtration rate; COPD = chronic obstructive pulmonary disease; SpO2 = oxygen saturation. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 2

Cytokine profile of all COVID-19 patients at baseline and according to the outcome.

Cytokines, pg/mL	All patients (n=94)	ICU-free and alive at D14 (n=77)	ICU admission or death at D14 (n=17)
IL-8	45.1 [32.53–73.26]	43.6 [30.74–62.97]	68.9 [49.14–95.6]*
IL-6	26.6 [9.67–50.85]	18.1 [8.96–41.91]	60.4 [30.14–222.5]*
TNF	16.9 [13.4–21.7]	16.4 [12.99–20.27]	19.2 [15.47–38.07]**
IL-10	7.4 [3.86–13.21]	6.1 [3.46–10.68]	12.8 [8.45–15.5]**
IL-22	2.1 [1.11–3.71]	1.8 [1.12–3.48]	3.3 [0.81–6.3]
IFN γ	0.6 [0.14–1.87]	0.7 [0.14–2.08]	0.3 [0.23–0.66]
IL-4	0.3 [0.19–0.76]	0.3 [0.19–0.82]	0.3 [0.17–0.66]
IL-5	0.2 [0.09–0.4]	0.2 [0.09–0.4]	0.2 [0.09–0.43]
IL-1 β	0.2 [0.1–0.32]	0.2 [0.1–0.31]	0.2 [0.14–0.33]
IL-12p70	0.2 [0.09–0.3]	0.2 [0.09–0.31]	0.2 [0.13–0.25]
IL-2	0 [0–1.4]	0 [0–1.6]	0 [0–0]**
IFN β	0 [0–0.69]	0 [0–0.69]	0 [0–0.9]

Cytokine profile of 94 COVID-19 patients, and comparison between ICU-free and alive patients versus those admitted to ICU or dead by day 14 of follow-up. All cytokines were measured using SP-X (Simoa Planar Technology; Human 10-Plex, Quanterix®, Netherlands), except IL-2 (ProcartaPlex, ThermoFisher®, Life Technologies SAS, Villebon sur Yvette, France) and IFN- β (ELISA, VeriKine-HS). Data are presented as median [interquartile range]. Comparison was made using Mann-Whitney's test. P value <0.05 was considered statistically significant. *P<0.01; **P<0.05

shown to partially rescue immune dysregulation both *in vitro* and *in vivo* [4]. Beyond, prospective observational data shows promising results [5], while results from several randomized clinical trials are eagerly awaited. Based on our findings and on others studies [6,7,8], another potential target would be TNF [2,9]. Despite the known deleterious effect in septic shock [1], observational data from inflammatory bowel disease patients on TNF blockers showed interesting results [9]. So far, anti-TNF has received less attention than anti-IL6 in COVID-19.

In conclusion, cytokine profiling at baseline can predict short-term outcomes, and thus could be used to choose proper candidates for directed-targeted therapies. Ongoing randomized clinical trials testing disease-modifying anti-rheumatic drugs will provide important answers, while testing baseline cytokine levels could be considered in patient enrolment.

Disclosure of interest

The authors declare that they have no competing interest.

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